The Comparative In Vitro Activity of FK-037 (Cefoselis), a New Broad-Spectrum Cephalosporin

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FK–037, a new parenteral cephalosporin, was active against clinical isolates of both gram-positive and gram-negative aerobic bacteria. The activity of FK–037 was similar to that of cefpirome and cefepime and generally superior to that of ceftazidime. Methicillin-resistant staphylococci were less susceptible than methicillin-sensitive isolates but most remained within the sensitive range. All streptococci and Enterobacteriaceae were sensitive as were the majority of isolates of Acinetobacter spp. and Pseudomonas aeruginosa. There was resistance amongst other non-fermentative gram-negative bacilli but this was species specific and most pseudomonads were sensitive, with resistance seen in Stenotrophomonas maltophilia, Alcaligenes spp. and Flavobacterium spp.

FK–037 is a new parenteral oxime-type cephem which, like other β-lactam antibiotics, inhibits bacterial cell division by inactivation of enzymes involved in cell wall synthesis. Structural modifications of the cephem nucleus have produced a variety of cephalosporins which show increased stability to β-lactamases and increased activity against gram-negative bacteria but somewhat decreased activity against gram-positive bacteria. Recent advances have produced agents such as cefpirome and cefepime with a much broader spectrum of activity including gram-positive organisms (1). Preliminary studies (2, 3) and subsequent more detailed in vitro studies (4, 5) have shown that FK–037, which contains a 1-hydroxyethyl-5-amino pyrazoliomethyl moiety at position three of the cephem ring, has good activity against streptococci and staphylococci, including methicillin-resistant isolates, and is stable to most β-lactamases.

We have studied the in vitro activity of FK–037 compared with that of cefepime, cefpirome, ceftazidime, meropenem, gentamicin and ciprofloxacin against clinical isolates of common gram-positive and gram-negative aerobic bacteria.

Materials and Methods

Organisms

The strains included in the study were all clinical isolates from St. Thomas' Hospital and were selected to include representative numbers of the different species, some of which were known to be resistant to many of the agents tested, including those with acquired aminoglycoside and quinolone resistance, hyperproduction of chromosomal β-lactamases in Enterobacteriaceae and pseudomonads and plasmid-mediated β-lactamases but no Enterobacteriaceae with extended spectrum β-lactamases were included since these do not occur in our patients. Isolates were identified by routine laboratory methods.

Antimicrobial agents

The agents tested, gifts of the manufacturers supplied as powders of known potency, were FK–037 (R.W. Johnson Pharmaceutical Research Institute), cefepime (Bristol Myers), cefpirome and gentamicin (Roussel Laboratories), ceftazidime (Glaxo), meropenem (Zenica) and ciprofloxacin (Bayer UK).

Determination of minimum inhibitory concentrations (MICs)

An agar dilution method was used and plates were inoculated with a 37-pin multipoint inoculator (Denley). The medium was Diagnostic Sensitivity Test agar (Oxoid CM261) supplemented with 5% saponin-lysed horse blood for the testing of streptococci. The bacteria were either grown in brain heart infusion broth (Oxoid CM266) or, in the case of streptococci, suspended in broth from fresh agar cultures and diluted to give a final inoculum of 10^4–10^5 CFU per spot. The plates were incubated overnight at 37°C in air (with 5% CO_2 for *Streptococcus pneumoniae*) or at 35°C for staphylococci. *Escherichia coli* NCTC 10418 (FK–037 MIC: 0.016 mg/l), *Pseudomonas aeruginosa* NCTC 10662 (FK–037 MIC: 2 mg/l) and *Staphylo-*

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Table 1 In vitro activity against gram-positive cocci

Organism (number tested)	*Compound*	*MIC (mg/l)* Range	MIC_{50}	MIC_{90}
Staphylococcus aureus	FK–037	0.5 – 4	1	2
methicillin-sensitive (32)	cefepime	0.5 – 2	0.5	1
	cefpirome	0.25 – 2	0.5	1
	ceftazidime	4 – 32	8	8
	meropenem	0.06 – 0.5	0.125	0.125
	gentamicin	0.125 – 128	0.25	0.5
	ciprofloxacin	0.125 – 2	0.25	1
Staphylococcus aureus	FK–037	4 – 8	4	8
methicillin-resistant (9)	cefepime	2 – 8	4	8
	cefpirome	2 – 8	2	8
	ceftazidime	16 – 32	32	32
	meropenem	0.5 – 1	1	1
	gentamicin	0.25 – 128	1	128
	ciprofloxacin	0.125 – 0.5	0.5	0.5
Staphylococcus saprophyticus	FK–037	0.5 – 1	1	1
(20)	cefepime	0.5 – 2	2	2
	cefpirome	0.25 – 1	1	1
	ceftazidime	8 – 32	16	32
	meropenem	0.06 – 0.5	0.25	0.25
	gentamicin	0.008 – 0.03	0.016	0.016
	ciprofloxacin	0.25 – 0.5	0.5	0.5
Coagulase-negative methicillin-	FK–037	0.125 – 4	0.5	1
sensitive staphylococci	cefepime	0.125 – 4	0.5	2
(30)	cefpirome	0.125 – 2	0.25	1
	ceftazidime	4 – 64	8	16
	meropenem	0.03 – 4	0.125	2
	gentamicin	0.016 – 32	0.125	16
	ciprofloxacin	0.06 – 1	0.25	0.5
Coagulase-negative methicillin-	FK–037	0.25 – 16	2	8
resistant staphylococci	cefepime	1 – 64	2	32
(16)	cefpirome	0.5 – 64	1	16
	ceftazidime	8 – >128	32	128
	meropenem	0.06 – 32	2	16
	gentamicin	0.016 – 128	8	128
	ciprofloxacin	0.25 – 8	0.25	0.5
Streptococcus pneumoniae	FK–037	0.008 – 0.5	0.016	0.25
(41)	cefepime	0.016 – 1	0.03	1
	cefpirome	0.008 – 1	0.03	0.25
	ceftazidime	0.06 – 8	0.25	8
	meropenem	0.002 – 1	0.008	0.25
	ciprofloxacin	0.5 – 8	2	4
ß-hemolytic streptococci	FK–037	0.004 – 0.008	0.008	0.008
Groups A, C & G (40)	cefepime	0.008 – 0.03	0.016	0.03
	cefpirome	0.004 – 0.016	0.008	0.016
	ceftazidime	0.03 – 0.25	0.125	0.25
	meropenem	0.004 – 0.016	0.008	0.016
	ciprofloxacin	0.25 – 4	0.5	1
Streptococcus agalactiae (25)	FK–037	0.016 – 0.03	0.03	0.03
	cefepime	0.06 – 0.125	0.06	0.125
	cefpirome	0.03 – 0.125	0.06	0.06
	ceftazidime	0.25 – 0.5	0.25	0.25
	meropenem	0.016 – 0.06	0.06	0.06
	ciprofloxacin	0.5 – 2	1	2

Table 2 In vitro activity against non-fastidious gram-negative bacilli

Organism (number tested)	*Compound*	*MIC (mg/l)* *Range*	*MIC_{50}*	*MIC_{90}*
Acinetobacter spp. (37)	FK–037	0.008 – 64	0.25	16
	cefepime	0.03 – 64	0.5	16
	cefpirome	0.016 – 32	0.125	32
	ceftazidime	0.06 – 16	1	16
	meropenem	0.004 – 2	0.06	0.5
	gentamicin	0.06 – >128	0.5	>128
	ciprofloxacin	0.008 – >128	0.06	1
Pseudomonas aeruginosa (56)	FK–037	0.5 – 32	2	8
	cefepime	0.5 – 32	2	16
	cefpirome	0.5 – 32	2	16
	ceftazidime	0.5 – 32	1	4
	meropenem	0.06 – 16	0.5	4
	gentamicin	0.125 – >128	1	64
	ciprofloxacin	0.06 – 128	0.25	8
Stenotrophomonas maltophilia (21)	FK–037	2 – 128	32	128
	cefepime	0.5 – 64	8	32
	cefpirome	1 – 128	32	128
	ceftazidime	0.5 – 64	8	32
	meropenem	2 – >128	8	64
	gentamicin	2 – >128	32	>128
	ciprofloxacin	0.25 – 16	2	4
Other non-fermenters* (46)	FK–037	0.125 – 128	2	32
	cefepime	0.06 – 64	4	32
	cefpirome	0.125 – 128	8	128
	ceftazidime	0.25 – 128	2	8
	meropenem	0.008 – 16	0.5	8
	gentamicin	0.06 – >128	1	>128
	ciprofloxacin	0.008 – 8	0.125	2
Escherichia coli (41)	FK–037	0.008 – 0.25	0.03	0.125
	cefepime	0.016 – 0.5	0.06	0.125
	cefpirome	0.03 – 0.5	0.06	0.125
	ceftazidime	0.008 – 8	0.125	0.5
	meropenem	0.008 – 0.03	0.016	0.03
	gentamicin	0.25 – 128	1	4
	ciprofloxacin	0.008 – 32	0.016	0.25
Klebsiella spp. (35)	FK–037	0.004 – 0.25	0.03	0.125
	cefepime	0.016 – 0.25	0.06	0.125
	cefpirome	0.016 – 0.5	0.03	0.25
	ceftazidime	0.06 – 1	0.125	0.5
	meropenem	0.016 – 0.06	0.03	0.03
	gentamicin	0.25 – >128	0.5	128
	ciprofloxacin	0.008 – 2	0.03	0.25
Citrobacter spp. (40)	FK–037	0.016 – 0.5	0.03	0.25
	cefepime	0.016 – 0.25	0.03	0.125
	cefpirome	0.016 – 0.5	0.03	0.25
	ceftazidime	0.06 – 16	0.25	0.5
	meropenem	0.016 – 0.06	0.03	0.03
	gentamicin	0.25 – 16	0.5	8
	ciprofloxacin	0.002 – 0.25	0.008	0.03

Table 2 (continued)

Organism (number tested)	*Compound*	*MIC (mg/l)* Range	MIC_{50}	MIC_{90}
Serratia spp. (25)	FK–037	0.06 – 0.5	0.125	0.25
	cefepime	0.03 – 0.25	0.125	0.25
	cefpirome	0.03 – 0.25	0.06	0.125
	ceftazidime	0.06 – 0.5	0.125	0.25
	meropenem	0.03 – 0.06	0.03	0.06
	gentamicin	0.125 – 64	0.5	16
	ciprofloxacin	0.03 – 0.25	0.06	0.125
Enterobacter spp. (62)	FK–037	0.016 – 8	0.06	0.25
	cefepime	0.016 – 2	0.06	0.25
	cefpirome	0.016 – 4	0.06	0.25
	ceftazidime	0.06 – 64	0.25	2
	meropenem	0.008 – 0.25	0.03	0.125
	gentamicin	0.125 – 64	0.5	8
	ciprofloxacin	0.008 – 32	0.016	0.06
Hafnia alvei (20)	FK–037	0.016 – 0.125	0.03	0.06
	cefepime	0.016 – 0.06	0.03	0.06
	cefpirome	0.016 – 0.125	0.03	0.06
	ceftazidime	0.25 – 4	1	2
	meropenem	0.016 – 0.03	0.016	0.03
	gentamicin	0.25 – 1	0.5	1
	ciprofloxacin	0.004 – 0.016	0.008	0.016
Proteus spp. (65)	FK–037	0.03 – 0.125	0.03	0.06
	cefepime	0.03 – 0.5	0.06	0.125
	cefpirome	0.06 – 0.5	0.125	0.25
	ceftazidime	0.008 – 0.25	0.06	0.125
	meropenem	0.03 – 0.5	0.125	0.25
	gentamicin	0.06 – 16	1	4
	ciprofloxacin	0.004 – 0.5	0.03	0.06
Providencia spp. (74)	FK–037	0.004 – 8	0.06	0.5
	cefepime	0.008 – 1	0.06	0.125
	cefpirome	0.008 – 4	0.125	0.5
	ceftazidime	0.008 – 4	0.25	1
	meropenem	0.016 – 0.25	0.06	0.125
	gentamicin	0.125 – >128	2	64
	ciprofloxacin	0.004 – 2	0.06	1
Morganella morganii (21)	FK–037	0.016 – 0.125	0.03	0.06
	cefepime	0.016 – 0.25	0.03	0.06
	cefpirome	0.016 – 0.25	0.03	0.06
	ceftazidime	0.03 – 4	0.125	1
	meropenem	0.03 – 0.125	0.06	0.125
	gentamicin	0.25 – 128	0.5	8
	ciprofloxacin	0.008 – 8	0.016	0.06

**Alcaligenes* spp. (4 isolates), *Comamonas acidovorans* (11), *Flavobacterium* spp. (2), *Burkholderia cepacia* (2), *Pseudomonas fluorescens* (10) *Pseudomonas putida* (10), *Pseudomonas stutzeri* (4), and one isolate each of *Achromobacter xylosoxidans, Agrobacterium radiobacter* and *Ochrobactrum anthropi*

coccus aureus NCTC 6571 (FK–037 MIC: 0.5 mg/l) were included as control strains.

Results and discussion

Comparative MICs against gram-positive bacteria are shown in Table 1. The activity of FK–037 was similar to that of cefpirome and cefepime, the two other fourth generation cephalosporins tested, and superior to that of ceftazidime against all staphylococci at 35°C, the temperature used for testing. Methicillin-sensitive staphylococci were more sensitive to all the β-lactam antibiotics than were methicillin-resistant strains. However, when a breakpoint of 8 mg/l was employed for

FK–037, the majority of staphylococci fell within the sensitive range as for cefepime and cefpirome but it remains to be proven to be effective in vivo. The majority of *Staphylococcus aureus* isolates were also sensitive in vitro to meropenem but many methicillin-resistant coagulase-negative staphylococci were resistant. Ceftazidime was 4 to 8-fold less active than FK–037 against methicillin-sensitive staphylococci and all methicillin-resistant isolates were resistant to ceftazidime.

FK–037, like cefepime, cefpirome and meropenem, was highly active against *Streptococcus pneumoniae.* Although penicillin-resistant isolates (penicillin MICs: 0.25–2 mg/l) were less sensitive they were still well within the conventional sensitive range (FK–037 MICs: 0.06–0.5 mg/l): there was an excellent correlation of MICs of the two compounds (r=0.95). All the β-lactams were active against β-haemolytic streptococci but ceftazidime was the least active of these agents, as it was for most gram-positive bacteria.

Comparative activity against non-fastidious gram-negative bacilli is shown in Table 2. The activity of all the cephalosporins was similar against *Acinetobacter* spp., which were not further identified, and they were less active than meropenem, the only agent to which none of the isolates were resistant. All the β-lactams were active against most isolates of *Pseudomonas aeruginosa* but none of them had good activity against *Stenotrophomonas maltophilia.* There were isolates resistant to FK–037 amongst the other non-fermentative gram-negative aerobes as there were to all the agents tested but resistance to the β-lactams was generally species-specific. All the pseudomonads tested were sensitive to FK–037 (MICs: 0.5–8 mg/l for *Pseudomonas fluorescens, Pseudomonas putida* and *Burkholderia cepacia* and 0.125–0.25 mg/l for *Pseudomonas stutzeri*) as were half the isolates of *Comamonas acidovorans* and the one isolate of *Agrobacterium radiobacter* but the remainder of the isolates, including all the *Alcaligenes* spp., both *Flavobacterium* spp. and the single isolates of *Ochrobactrum anthropi* and *Achromobacter xylosoxidans* were resistant (FK–037 MICs: 16–128 mg/l). The range of activity of cefpirome and cefepime was similar to that of FK–037 against these isolates but ceftazidime was more active and all the *Comamonas acidovorans* and *Alcaligenes* spp. were sensitive. Both isolates of *Flavobacterium* spp. were resistant to meropenem and all other species were sensitive, though meropenem MICs for *Pseudomonas fluorescens* and *Pseudomonas putida* were close to the breakpoint.

FK–037, like cefpirome and cefepime, was highly active against Enterobacteriaceae including strains known to produce plasmid-mediated and chromosomal β-lactamases. The one exception was a strain of *Enterobacter cloacae* with derepressed chromosomal β-lactamase which was resistant to ceftazidime (MIC: 64 mg/l) and also had decreased sensitivity to FK–037 (MIC: 8 mg/l) and to cefpirome and cefepime (MIC: 4 mg/l). There was little difference between the three agents except against *Proteus* spp. and *Providencia* spp. for which cefpirome was the least active and FK–037 the most active of these three. There was one isolate of *Providencia stuartii* with decreased sensitivity to FK–037 (MIC: 8 mg/l) and to cefpirome (MIC: 4 mg/l) but this isolate was more sensitive to ceftazidime and cefepime (MIC for both agents: 1 mg/l).

There was no evidence of cross-resistance between FK–037 and gentamicin or ciprofloxacin against either gram-positive or gram-negative bacteria although a few multi-resistant isolates were amongst the least sensitive to FK–037 and the other cephalosporins.

Our results have shown, like those of other workers (4, 5) that FK–037 is a promising new stable broad spectrum cephalosporin, that, like cefpirome and cefepime, it is more active in vitro than ceftazidime against most isolates, and that there appears to be little or no effect on FK–037 by the commonly encountered β-lactamases. If pharmacological and animal studies indicate, assessment for clinical use is warranted.

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